

## WHAT IS CLAIMED IS:

1. A method for synthesizing procyanidin B2 comprising the steps of:
  - a) esterification of an epicatechin to form a 5, 7, 3', 4', 3'' – penta-O-acyl-epicatechin;
  - b) protecting the 5, 7, 3', 4', 3'' – penta-O-acyl-epicatechin to form a 5, 7, 3', 4'– tetra-O-protected epicatechin;
  - c) coupling an adduct precursor with a first portion of the 5, 7, 3', 4'– tetra-O-protected epicatechin to form a 4''-substituted, 5, 7, 3', 4'– tetra-O-protected epicatechin;
  - d) dimerizing a second portion of the 5, 7, 3', 4'– tetra-O-protected epicatechin with the 4''-substituted, 5, 7, 3', 4'– tetra-O-protected epicatechin to form a 5, 7, 3', 4'-tetra-O-protected epicatechin-4 $\beta$   $\rightarrow$  8-5,7,3',4'-tetra-O-protected epicatechin; and
  - e) deprotecting the 5, 7, 3', 4'-tetra-O-protected epicatechin-4 $\beta$   $\rightarrow$  8-5,7,3',4'-tetra-O-protected epicatechin to form procyanidin B2.
2. The method of claim 1, wherein the esterification step comprises the step of acetylation of an epicatechin to form a 5, 7, 3', 4', 3'' – penta-O-acetyl-epicatechin.
3. The method of claim 1, wherein the protection step comprises the step of protecting the 5, 7, 3', 4', 3'' – penta-O-acyl-epicatechin to form a 5, 7, 3', 4'– tetra-O-benzylepicatechin.
4. The method of claim 3, wherein the protecting step comprises the step of reacting the 5, 7, 3', 4', 3'' – penta-O-acyl-epicatechin with benzylchloride in the presence of water to form the 5, 7, 3', 4'– tetra-O-benzylepicatechin.
5. The method of claim 4, wherein the protecting step comprises the step of reacting the 5, 7, 3', 4', 3'' – penta-O-acyl-epicatechin with between about 4.0 and about 4.2 equivalents of benzylchloride for between about 24 hours and about 72 hours to form a reaction mixture comprising the 5, 7, 3', 4'– tetra-O-benzylepicatechin.
6. The method of claim 5, wherein the protecting step comprises the step of combining the reaction mixture with an acid.
7. The method of claim 6, wherein the reaction mixture is combined with hydrochloric acid.
8. The method of claim 7, wherein the hydrochloric acid is between about 0.01 M and about 3 M.
9. The method of claim 7, wherein the hydrochloric acid is between about -10°C and about +10°C.

10. The method of claim 4, wherein the protecting step comprises the steps of:
  - a) reacting the 5, 7, 3', 4', 3'' – penta-O-acyl-epicatechin with between about 4.0 and about 4.2 equivalents of benzylchloride for between about 24 hours and about 72 hours in the presence of water to form a reaction mixture comprising the 5, 7, 3', 4'– tetra-O-benzylepicatechin; and
  - b) combining the reaction mixture with hydrochloric acid, wherein the hydrochloric acid is between about 0.01 M and about 3 M, and between about -10°C and about +10°C.
11. The method of claim 1, wherein the coupling step comprises the step of coupling an ethylene glycol with the first portion of the 5, 7, 3', 4'– tetra-O-protected epicatechin to form a 5, 7, 3', 4'– tetra-O-protected 4-(2-hydroxyethoxy)epicatechin.
12. The method of claim 1, wherein the dimerization step comprises the steps of:
  - a) crystallizing the 5, 7, 3', 4'–tetra-O-protected epicatechin-4 $\beta$   $\rightarrow$  8-5,7,3',4'–tetra-O-protected epicatechin; and
  - b) isolating the 5, 7, 3', 4'–tetra-O-protected epicatechin-4 $\beta$   $\rightarrow$  8-5,7,3',4'–tetra-O-protected epicatechin using column chromatography.
13. A method for synthesizing procyanidin B2 comprising the steps of:
  - a) acetylation of an epicatechin to form a 5, 7, 3', 4', 3'' – penta-O-acetyl-epicatechin;
  - b) reacting the 5, 7, 3', 4', 3'' – penta-O-acetyl-epicatechin with between about 4.0 and about 4.2 equivalents of benzylchloride for between about 24 hours and about 72 hours in the presence of water to form a reaction mixture comprising a 5, 7, 3', 4'– tetra-O-benzylepicatechin;
  - c) combining the reaction mixture with hydrochloric acid to form purified 5, 7, 3', 4'– tetra-O-benzylepicatechin, wherein the hydrochloric acid is between about 0.01 M and about 3 M, and between about -10°C and about 10°C;
  - d) coupling an ethylene glycol with a first portion of the purified 5, 7, 3', 4'– tetra-O-benzylepicatechin to form a 5, 7, 3', 4'– tetra-O-benzyl-4-(2-hydroxyethoxy)epicatechin;
  - e) dimerizing a second portion of the 5, 7, 3', 4'– tetra-O-benzylepicatechin with the 5, 7, 3', 4'– tetra-O-benzyl-4-(2-hydroxyethoxy)epicatechin to form a 5, 7, 3', 4'–tetra-O-benzylepicatechin-4 $\beta$   $\rightarrow$  8-5,7,3',4'–tetra-O-benzylepicatechin;

- f) crystallizing the 5, 7, 3', 4'-tetra-O-benzylepicatechin-4 $\beta$   $\rightarrow$  8-5,7,3',4'-tetra-O-benzylepicatechin;
  - g) isolating the 5, 7, 3', 4'-tetra-O-benzylepicatechin-4 $\beta$   $\rightarrow$  8-5,7,3',4'-tetra-O-benzylepicatechin using column chromatography; and
  - h) deprotecting the 5, 7, 3', 4'-tetra-O-benzylepicatechin-4 $\beta$   $\rightarrow$  8-5,7,3',4'-tetra-O-benzylepicatechin to form procyanidin B2.
14. A method for synthesizing a 5, 7, 3', 4' – tetra-O-protected epicatechin comprising the steps of:
- a) esterification of an epicatechin to form a 5, 7, 3', 4', 3" – penta-O-acyl-epicatechin; and
  - b) protecting the 5, 7, 3', 4', 3" – penta-O-acyl-epicatechin to form a 5, 7, 3', 4' – tetra-O-protected epicatechin.
15. A method for isolating procyanidin B2 comprising the steps of:
- a) extracting a sample of bark powder from plant matter of the genus *Uncaria* with an alcohol to form an extract;
  - b) fractionating the extract using flash vacuum fractionation to form a plurality of flash vacuum fractions of extract and analyzing the plurality of flash vacuum fractions to determine the flash vacuum fractions comprising procyanidin B2;
  - c) fractionating at least one of the flash vacuum fractions comprising procyanidin B2 using silica gel column chromatography to form a plurality of silica gel fractions and analyzing the plurality of silica gel fractions to determine the silica gel fractions comprising procyanidin B2;
  - d) fractionating at least one of the silica gel fractions comprising procyanidin B2 using Sephadex LH20 column chromatography to form a plurality of Sephadex LH20 fractions.
16. The method of claim 15, wherein the extraction step comprises the steps of
- a) stirring a mixture of the sample of bark powder from plant matter of the genus *Uncaria* and methanol; and
  - b) filtering the mixture to obtain a filtrate.
17. The method of claim 16, comprising the step of allowing the stirred mixture to settle prior to filtration.

18. The method of claim 16, comprising the step of centrifuging the stirred mixture prior to filtration.
19. The method of claim 15, wherein the flash vacuum fractionation step comprises the step of analyzing the plurality of flash vacuum fractions by a technique selected from the group consisting of thin layer chromatography (TLC) and high pressure liquid chromatography (HPLC).
20. The method of claim 15, wherein the silica gel fractionation step comprises the step of analyzing the plurality of silica gel fractions by a technique selected from the group consisting of thin layer chromatography (TLC) and high pressure liquid chromatography (HPLC).
21. The method of claim 15, wherein the Sephadex LH20 fractionation step comprises the step of analyzing the plurality of Sephadex LH20 fractions by a technique selected from the group consisting of thin layer chromatography (TLC) and high pressure liquid chromatography (HPLC).
22. A method for treating the formation, deposition, accumulation, or persistence of amyloid fibrils, comprising the step of treating the fibrils with an effective amount of a procyanidin B2 synthesized according to claim 1.
23. The method of claim 22, wherein the amyloid fibrils are A $\beta$  amyloid fibrils.
24. The method of claim 22, wherein the amyloid fibrils are IAPP amyloid fibrils.
25. A method for treating the formation, deposition, accumulation, or persistence of synuclein fibrils, comprising the step of treating the fibrils with an effective amount of a procyanidin B2 synthesized according to claim 1.
26. The method of claim 25, wherein the synuclein fibrils are  $\alpha$ -synuclein fibrils.
27. A method for treating an amyloid disease or a synucleinopathy in a mammal, comprising the step of administering a therapeutically effective amount of a procyanidin B2 synthesized according to claim 1 to the mammal.
28. The method of claim 27, wherein the amyloid disease is a disease associated with the formation, deposition, accumulation, or persistence of an amyloid protein selected from the group consisting of A $\beta$  amyloid, AA amyloid, AL amyloid, IAPP amyloid,  $\alpha_2$ -microglobulin amyloid, transthyretin, prealbumin, and procalcitonin.
29. The method of claim 28, wherein the amyloid disease is a disease associated with the formation, deposition, accumulation, or persistence of A $\beta$  amyloid.

30. The method of claim 28, wherein the amyloid disease is a disease associated with the formation, deposition, accumulation, or persistence of IAPP amyloid.
31. The method of claim 27, wherein the amyloid disease is selected from the group of diseases consisting of Alzheimer's disease, Down's syndrome, dementia pugilistica, multiple system atrophy, inclusion body myositis, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, Nieman-Pick disease type C, cerebral  $\beta$ -amyloid angiopathy, dementia associated with cortical basal degeneration, the amyloidosis of type 2 diabetes, the amyloidosis of chronic inflammation, the amyloidosis of malignancy and Familial Mediterranean Fever, the amyloidosis of multiple myeloma and B-cell dyscrasias, the amyloidosis of the prion diseases, Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome, kuru, scrapie, the amyloidosis associated with carpal tunnel syndrome, senile cardiac amyloidosis, familial amyloidotic polyneuropathy, and the amyloidosis associated with endocrine tumors.
32. The method of claim 31, wherein the amyloid disease is Alzheimer's disease.
33. The method of claim 27, wherein the synucleinopathy is a disease associated with the formation, deposition, accumulation, or persistence of synuclein fibrils.
34. The method of claim 33, wherein the synucleinopathy is a disease associated with the formation, deposition, accumulation, or persistence of  $\alpha$ -synuclein fibrils.
35. The method of claim 27, wherein the synucleinopathy is selected from the group of diseases consisting of Parkinson's disease, familial Parkinson's disease, Lewy body disease, the Lewy body variant of Alzheimer's disease, dementia with Lewy bodies, multiple system atrophy, and the Parkinsonism-dementia complex of Guam.
36. The method of claim 35, wherein the synucleinopathy is Parkinson's disease.
37. The method of claim 27, wherein the mammal is a human.
38. The method of claim 27, wherein the amount of the procyanidin B2 administered is between about 0.1 mg/kg of body weight per day and about 1000 mg/kg of body weight per day.
39. The method of claim 27, wherein the amount of the procyanidin B2 administered is between about 1 mg/kg of body weight per day and about 100 mg/kg of body weight per day.
40. The method of claim 27, wherein the amount of the procyanidin B2 administered is between about 10 mg/kg of body weight per day and about 100 mg/kg of body weight per

day.

41. A method for treating the formation, deposition, accumulation, or persistence of amyloid fibrils, comprising the step of treating the fibrils with an effective amount of a procyanidin B2 isolated according to claim 15.
42. The method of claim 41, wherein the amyloid fibrils are A $\beta$  amyloid fibrils.
43. The method of claim 41, wherein the amyloid fibrils are IAPP amyloid fibrils.
44. A method for treating the formation, deposition, accumulation, or persistence of synuclein fibrils, comprising the step of treating the fibrils with an effective amount of a procyanidin B2 isolated according to claim 15.
45. The method of claim 44, wherein the synuclein fibrils are  $\alpha$ -synuclein fibrils.
46. A method for treating an amyloid disease or a synucleinopathy in a mammal, comprising the step of administering a therapeutically effective amount of a procyanidin B2 isolated according to claim 15 to the mammal.
47. The method of claim 46, wherein the amyloid disease is a disease associated with the formation, deposition, accumulation, or persistence of an amyloid protein selected from the group consisting of A $\beta$  amyloid, AA amyloid, AL amyloid, IAPP amyloid,  $\alpha_2$ -microglobulin amyloid, transthyretin, prealbumin, and procalcitonin.
48. The method of claim 47, wherein the amyloid disease is a disease associated with the formation, deposition, accumulation, or persistence of A $\beta$  amyloid.
49. The method of claim 47, wherein the amyloid disease is a disease associated with the formation, deposition, accumulation, or persistence of IAPP amyloid.
50. The method of claim 46, wherein the amyloid disease is selected from the group of diseases consisting of Alzheimer's disease, Down's syndrome, dementia pugilistica, multiple system atrophy, inclusion body myositis, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, Nieman-Pick disease type C, cerebral  $\beta$ -amyloid angiopathy, dementia associated with cortical basal degeneration, the amyloidosis of type 2 diabetes, the amyloidosis of chronic inflammation, the amyloidosis of malignancy and Familial Mediterranean Fever, the amyloidosis of multiple myeloma and B-cell dyscrasias, the amyloidosis of the prion diseases, Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome, kuru, scrapie, the amyloidosis associated with carpal tunnel syndrome, senile cardiac amyloidosis, familial amyloidotic polyneuropathy, and the amyloidosis associated with

endocrine tumors.

51. The method of claim 50, wherein the amyloid disease is Alzheimer's disease.

52. The method of claim 46, wherein the synucleinopathy is a disease associated with the formation, deposition, accumulation, or persistence of synuclein fibrils.

53. The method of claim 52, wherein the synucleinopathy is a disease associated with the formation, deposition, accumulation, or persistence of  $\alpha$ -synuclein fibrils.

54. The method of claim 46, wherein the synucleinopathy is selected from the group of diseases consisting of Parkinson's disease, familial Parkinson's disease, Lewy body disease, the Lewy body variant of Alzheimer's disease, dementia with Lewy bodies, multiple system atrophy, and the Parkinsonism-dementia complex of Guam.

55. The method of claim 54, wherein the synucleinopathy is Parkinson's disease.

56. The method of claim 46, wherein the mammal is a human.

57. The method of claim 46, wherein the amount of the procyanidin B2 administered is between about 0.1 mg/kg of body weight per day and about 1000 mg/kg of body weight per day.

58. The method of claim 46, wherein the amount of the procyanidin B2 administered is between about 1 mg/kg of body weight per day and about 100 mg/kg of body weight per day.

59. The method of claim 46, wherein the amount of the procyanidin B2 administered is between about 10 mg/kg of body weight per day and about 100 mg/kg of body weight per day.

60. A pharmaceutical composition comprising:

- a) a procyanidin B2 synthesized according to claim 1; and
- b) a pharmaceutically acceptable pharmaceutically acceptable excipient.

61. A pharmaceutical composition comprising:

- a) a procyanidin B2 isolated according to claim 15; and
- b) a pharmaceutically acceptable excipient.

62. Use of a procyanidin B2 synthesized according to claim 1 in the manufacture of a medicament for treating the formation, deposition, accumulation, or persistence of amyloid fibrils.

63. The use of claim 62, wherein the amyloid fibrils are A $\beta$  amyloid fibrils.

64. The use of claim 62, wherein the amyloid fibrils are IAPP amyloid fibrils.

65. Use of a procyanidin B2 synthesized according to claim 1 in the manufacture of a medicament for treating the formation, deposition, accumulation, or persistence of synuclein fibrils.
66. The use of claim 65, wherein the synuclein fibrils are  $\alpha$ -synuclein fibrils.
67. Use of procyanidin B2 synthesized according to claim 1 in the manufacture of a medicament for treating an amyloid disease or a synucleinopathy in a mammal.
68. The use of claim 67, wherein the amyloid disease is a disease associated with the formation, deposition, accumulation, or persistence of an amyloid protein selected from the group consisting of A $\beta$  amyloid, AA amyloid, AL amyloid, IAPP amyloid,  $\alpha_2$ -microglobulin amyloid, transthyretin, prealbumin, and procalcitonin.
69. The use of claim 68, wherein the amyloid disease is a disease associated with the formation, deposition, accumulation, or persistence of A $\beta$  amyloid.
70. The use of claim 68, wherein the amyloid disease is a disease associated with the formation, deposition, accumulation, or persistence of IAPP amyloid.
71. The use of claim 67, wherein the amyloid disease is selected from the group of diseases consisting of Alzheimer's disease, Down's syndrome, dementia pugilistica, multiple system atrophy, inclusion body myositis, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, Nieman-Pick disease type C, cerebral  $\beta$ -amyloid angiopathy, dementia associated with cortical basal degeneration, the amyloidosis of type 2 diabetes, the amyloidosis of chronic inflammation, the amyloidosis of malignancy and Familial Mediterranean Fever, the amyloidosis of multiple myeloma and B-cell dyscrasias, the amyloidosis of the prion diseases, Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome, kuru, scrapie, the amyloidosis associated with carpal tunnel syndrome, senile cardiac amyloidosis, familial amyloidotic polyneuropathy, and the amyloidosis associated with endocrine tumors.
72. The use of claim 71, wherein the amyloid disease is Alzheimer's disease.
73. The use of claim 67, wherein the synucleinopathy is a disease associated with the formation, deposition, accumulation, or persistence of synuclein fibrils.
74. The use of claim 73, wherein the synucleinopathy is a disease associated with the formation, deposition, accumulation, or persistence of  $\alpha$ -synuclein fibrils.
75. The use of claim 67, wherein the synucleinopathy is selected from the group of diseases consisting of Parkinson's disease, familial Parkinson's disease, Lewy body disease, the Lewy



body variant of Alzheimer's disease, dementia with Lewy bodies, multiple system atrophy, and the Parkinsonism-dementia complex of Guam.

76. The use of claim 75, wherein the synucleinopathy is Parkinson's disease.

77. Use of a procyanidin B2 isolated according to claim 15 in the manufacture of a medicament for treating the formation, deposition, accumulation, or persistence of amyloid fibrils.

78. The use of claim 77, wherein the amyloid fibrils are A $\beta$  amyloid fibrils.

79. The use of claim 77, wherein the amyloid fibrils are IAPP amyloid fibrils.

80. Use of a procyanidin B2 isolated according to claim 15 in the manufacture of a medicament for treating the formation, deposition, accumulation, or persistence of synuclein fibrils.

81. The use of claim 80, wherein the synuclein fibrils are  $\alpha$ -synuclein fibrils.

82. Use of a procyanidin B2 isolated according to claim 15 in the manufacture of a medicament for treating an amyloid disease or a synucleinopathy in a mammal.

83. The use of claim 82, wherein the amyloid disease is a disease associated with the formation, deposition, accumulation, or persistence of an amyloid protein selected from the group consisting of A $\beta$  amyloid, AA amyloid, AL amyloid, IAPP amyloid,  $\alpha_2$ -microglobulin amyloid, transthyretin, prealbumin, and procalcitonin.

84. The use of claim 83, wherein the amyloid disease is a disease associated with the formation, deposition, accumulation, or persistence of A $\beta$  amyloid.

85. The use of claim 83, wherein the amyloid disease is a disease associated with the formation, deposition, accumulation, or persistence of IAPP amyloid.

86. The use of claim 82, wherein the amyloid disease is selected from the group of diseases consisting of Alzheimer's disease, Down's syndrome, dementia pugilistica, multiple system atrophy, inclusion body myositis, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, Nieman-Pick disease type C, cerebral  $\beta$ -amyloid angiopathy, dementia associated with cortical basal degeneration, the amyloidosis of type 2 diabetes, the amyloidosis of chronic inflammation, the amyloidosis of malignancy and Familial Mediterranean Fever, the amyloidosis of multiple myeloma and B-cell dyscrasias, the amyloidosis of the prion diseases, Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome, kuru, scrapie, the amyloidosis associated with carpal tunnel syndrome, senile cardiac amyloidosis, familial amyloidotic

polyneuropathy, and the amyloidosis associated with endocrine tumors.

87. The use of claim 86, wherein the amyloid disease is Alzheimer's disease.

88. The use of claim 82, wherein the synucleinopathy is a disease associated with the formation, deposition, accumulation, or persistence of synuclein fibrils.

89. The use of claim 88, wherein the synucleinopathy is a disease associated with the formation, deposition, accumulation, or persistence of  $\alpha$ -synuclein fibrils.

90. The use of claim 82, wherein the synucleinopathy is selected from the group of diseases consisting of Parkinson's disease, familial Parkinson's disease, Lewy body disease, the Lewy body variant of Alzheimer's disease, dementia with Lewy bodies, multiple system atrophy, and the Parkinsonism-dementia complex of Guam.

91. The use of claim 90, wherein the synucleinopathy is Parkinson's disease.

92. A method for treating pain, inflammation, a viral infection, arthritis, rheumatism, bursitis, gout, an opportunistic infection, skin tumors and cysts, cancer, AIDs, Crohn's disease, a respiratory infection, an allergy, herpes, prostrate problems, lupus, Epstein Barr virus, chronic fatigue syndrome, and stomach and bowel disorders in a mammal, comprising the step of administering a therapeutically effective amount of a procyanidin B2 to the mammal.

93. Use of a procyanidin B2 in the manufacture of a medicament for treating pain, inflammation, a viral infection, arthritis, rheumatism, bursitis, gout, an opportunistic infection, skin tumors and cysts, cancer, AIDs, Crohn's disease, a respiratory infection, an allergy, herpes, prostrate problems, lupus, Epstein Barr virus, chronic fatigue syndrome, and stomach and bowel disorders in a mammal.

94. A product comprising:

- a) a procyanidin B2 synthesized according to claim 1; and
- b) a label indicating the intended method of treatment.

95. A product comprising:

- a) a procyanidin B2 isolated according to claim 15; and
- b) a label indicating the intended method of treatment.